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EXAMINER	
FOSTER, CHRISTINE E	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 10/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/661,790	YAMAZAKI ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,10 and 26-43* is/are pending in the application.

4a) Of the above claim(s) *26-33,37-39,41 and 43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,10,34-36,40 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/11/06 has been entered.

2. Applicant is reminded of the proper format for amendments to the claims. If a withdrawn claim is currently amended, its status in the claim listing may be identified as "withdrawn — currently amended. " See MPEP 714. Specifically, claims 26-33, 37-39 and 41 are accompanied by the status identifiers "currently amended" or "original" in the claim set filed 9/11/06, yet the claims were previously withdrawn from consideration (see the Office action mailed 5/9/06 and the requirement for restriction mailed 6/29/05).

Election/Restrictions

3. New claim 43 depends from independent claim 26, which is directed to a non-elected invention currently withdrawn from consideration (see the Office action mailed 5/9/06 and the requirement for restriction mailed 6/29/05). Accordingly, claim 43 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 7/29/05.

4. Claims 1-7, 10, and 26-43 are pending in the application, with claims 26-33, 37-39, 41, and 43 currently withdrawn. Claims 1-7, 10, 34-36, 40, and 42 are subject to examination below.

Information Disclosure Statement

An Information Disclosure Statement (IDS) has not been received. The Examiner notes that submission of an IDS is not required, but reminds Applicant of the duty to disclose information material to patentability (see 37 CFR 1.56).

Objections/Rejections Withdrawn

5. The objections to claims 1, 10, and 40 are withdrawn in response to the amendments.

6. The rejections of claims 4-7 under 112, 1st paragraph (new matter) set forth in the previous Office action (see p. 5-6) are withdrawn in response to the amendments to claim 4.

7. The rejections of claims 1 and 4-7 under 112, 2nd paragraph set forth in the previous Office action (see p. 13-15) are withdrawn in light of the amendments to claims 1 and 4.

8. The rejection of claim 36 under 112, 2nd paragraph for recitation of "cell-vesicle" is withdrawn in response to the deletion of this term from the claim.

9. The rejection of claim 36 under 112, 2nd paragraph for recitation of "giant vesicle" is withdrawn in response to Applicant's arguments that "giant vesicles" are well known in the art to refer to large unilamellar liposomes about 10 microns or greater (see p. 13).

10. The rejections of claims 1-7, 10, 4-36, and 40 under 35 USC 103(a) as being unpatentable over Boxer et al. in view of Groves et al. are withdrawn in response to the amendments to claim 1 to reflect that binding of the test agent is detected by detecting a decrease in membrane fluidity.

11. The rejections of claims 1-2, 4-7, 10, 34-36 and 40 under the doctrine of obviousness-type double patenting are withdrawn in response to the amendments to claim 1 discussed immediately above.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-7, 10, 34-36, and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New Matter

14. Claim 36 as amended recites that the test agent comprises "a plasma membrane vesicle", which represents a departure from the specification and claims as originally filed. The claim previously recited "a cell-vesicle". Applicant's response states that the term "plasma membrane vesicle" is well-known in the art (see p. 13) and asserts that no new matter has been added (p. 7) but does not specifically indicate where support may be found for this term in the specification. The examiner was unable to find the term "plasma membrane vesicle" disclosed in the specification. Since there is no evidence in the record that "plasma membrane vesicle" represents correction of the obvious error of "cell-vesicle" that would have been recognized as such by one skilled in the art, the amendment is deemed to represent new matter.

Written Description

15. Claims 1-7, 10, 34-36, and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The claims lack a written description for the following reasons. Independent claim 1 is drawn to a method for assaying an interaction between a test agent and a lipid bilayer-associated component, where binding is detected by detecting a decrease in membrane fluidity.

The claims encompass detection of binding by change in membrane fluidity between a genus of test agents to a genus of lipid bilayer-associated components. The genus of test agents is large and of substantial variance, and includes small molecules, cell surfaces, vesicles, lipid-covered glass beads, and other agents (see claims 34-36 and 42). The claimed genus of lipid bilayer-associated components that interact with test agents is also characterized by substantial variance, and includes proteins, nucleic acids, glycolipids, lipopolysaccharide, sterols, lipid-linked molecules, fatty acids, and endotoxins (claims 2-3). However, the claimed genera of test agents and lipid bilayer-associated components have no disclosed partial structure, shared physical and/or chemical properties, or shared functional or other relevant identifying characteristics. In particular, there is no disclosure of that the genera of test agents/lipid bilayer-associated components are known to affect physical properties of the bilayer upon interaction. *There is no disclosure of any relevant identifying characteristics shared by test agents/ lipid bilayer-associated components that have the capacity to decrease membrane fluidity upon binding.*

With regard to claims 34-36, there is no disclosure that small molecules, proteins other than cholera toxin subunit B (CTB), cells, vesicles, phantom cells, liposomes, giant vesicles,

lipid-covered glass beads, or "any component of any thereof" are known to affect the membrane fluidity of the bilayer upon interaction.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. The MPEP states that:

"The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice ...or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus" MPEP 2163.

In the instant case, the specification discloses only a single test agent (CTB) that is capable, upon interaction with a lipid bilayer-associated component (ganglioside GM1), of changing the membrane fluidity of the bilayer (see p. 23, lines 9-12 in particular). There are no working examples of other test agent-component pairs.

With regard to claim 3, there is no written description of a method for detecting the interaction of a test agent with bilayer-associated bacterial endotoxin by evaluating a physical property of the bilayer, as in claim 3. In Examples 3-4, 6 and in Figures 5C, 5D, 8, and 9, the

endotoxin CTB is the **test agent**, and not the **lipid bilayer-associated component** (see p. 25, lines 17-19 in particular). Example 5 discloses endotoxins as lipid bilayer-associated components in which test agents are screened for interaction (p. 31, line 23 to p. 32, line 2). However, this example appears to be prophetic, and there is no disclosure that the interaction of such agents with bilayer-associated endotoxins affects membrane fluidity of the bilayer.

Scope of Enablement

16. Claims 1-7, 10, 34-36, and 40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for while being enabling for assaying an interaction between test agents that are bacterial endotoxins such as CTB and lipid bilayer-associated components that are endotoxin receptors such as ganglioside GM1, or for assaying interactions using test agents that are antibodies, does not reasonably provide enablement for assaying an interaction with all test agent-component pairs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The nature of the invention relates to a method for assaying an interaction between a test agent and a lipid bilayer-associated component that is part of a substrate-supported bilayer. The method for assaying an interaction includes the step of contacting the device with the test agent, so as to allow the test agent to bind to its lipid bilayer-associated ligand. Binding is detected indirectly by evaluating membrane fluidity, where a decrease in membrane fluidity indicates that binding of the test agent to the lipid bilayer-associated component has occurred (see especially the specification at p. 14, lines 13-15 and p. 26, lines 3-14, which states that "[i]n accordance

with the present invention, binding events are detected through their effects on one or more physical properties of the lipid bilayer, such as membrane fluidity").

The claims are broadly drawn to methods of assaying binding between a large number of possible test agents and lipid bilayer-associated components, where the interaction is detected by evaluating the membrane fluidity. The genus of test agents is one of substantial variance, including such diverse species as small molecules (claim 34), proteins (claims 35 and 42), "a surface of a cell, a vesicle, a phantom cell, a plasma membrane vesicle, a liposome, a giant vesicle, a lipid-covered glass bead, or a component of any thereof" (claim 36). See also the specification at p. 3, lines 6-12, which discloses that test agents may include small molecules, polypeptides, antibodies, biomolecules, cell surfaces, vesicles, and phantom cells, for example.

The specification discloses CTB as an example of a test agent, which, upon binding to the lipid bilayer-associated ganglioside GM1, can affect the fluidity of lipid molecules in the neighborhood of the ganglioside (p. 14, line 33 to p. 15, line 4). The specification also provides working examples demonstrating that binding of CTB to membranes presenting GM1 may be detected indirectly by evaluating changes in membrane fluidity (Examples 3-4). The examples evaluate membrane fluidity by FRAP (Example 3) and by electrophoresis (Example 4).

The prior art teaches that the important feature in the interaction of CTB with ganglioside GM1 is *polyvalent binding*, as up to five GM1 receptors can bind to each cholera toxin molecule (Song et al., US Patent No. 6,297,059, column 8, lines 32-40 and column 6, lines 6-9). The interaction of cholera toxin with GM1 is therefore able to bring two or more GM1 receptors into close proximity (column 6, lines 1-5), which can be measured by fluorescence self-quenching or FRET (column 5, lines 49-51 and column 7, lines 44-67 in particular).

Therefore, unlike the large polyvalent CTB, binding of other test agents such as small molecules to bilayer-associated ligands would not necessarily have effects on membrane fluidity and other physical properties of the bilayer in light of the prior art teaching of the importance of polyvalent binding.

In fact, the prior art teaches that not all molecules decrease membrane fluidity upon binding. Moran et al. "Effect of Tocopherol and Taurine on Membrane Fluidity of Retinal Rod Outer Segments," (1987) Exp. Eye Res. **45**:769-776, the abstract and p. 775, lines 10-12) teach that the small molecule taurine has no effect on membrane fluidity upon interaction with membranes. See also Altstiel et al. ("Structural Changes in BHK Cell Plasma Membrane Caused by the Binding of Vesicular Stomatitis Virus" *Journal of Virology* (1981) Vol. 39, p. 82-86), which teaches that **"[l]igands that are monovalent or have reduced valency are generally unable to induce clustering of receptors in the plane of the plasma membrane"** (p. 82, right column). See also Paul et al. (US 5,770,570), which teaches that **"[b]inding of polypeptides by membranes can lead to qualitatively similar *or opposing effects* on fluidity at different depths in the bilayer"** (column 14, lines 23-31, emphasis added).

Binding of some test agents can also have the opposite effect of *increasing* membrane fluidity, as taught by Aguedo et al. ("Interaction of an odorant lactone with model phospholipids bilayers and its strong fluidizing action in yeast membrane" *International Journal of Food Microbiology* 80 (2003) 211-215), which teaches that interaction of γ-decalactone with a membrane-associated component (acyl chains of phospholipids) increases rather than decreases membrane fluidity (see especially the abstract and p. 214).

Thus, the prior art recognizes that not all test agents would be expected to cause a decrease in membrane fluidity upon binding to a lipid bilayer-associated component, and that some cause an increase in fluidity.

The specification provides no examples of test agents other than CTB that affect membrane fluidity or other physical properties upon binding. There are no working examples of other test agent/bilayer-associated component pairs that demonstrate such effects upon interaction.

The claims also encompass test agents interacting with lipid bilayer-associated integral membrane proteins. The prior art teaches that integral membrane proteins in supported bilayers may often be non-functional, and therefore incapable of interacting with test agents. Boxer et al. teach that:

> [I]ntegral membrane proteins are immobile or exhibit severely restriction motion in supported bilayers. It is presumed that this is a result of interactions between the membrane protein and the solid support; there have been relatively few careful studies of the functional consequences of this interaction, but it is generally thought that these interactions will reduce or eliminate protein function.

See Boxer et al., "Molecular transport and organization in supported lipid membranes" (2000) Curr. Opin. Chem. Biol. **4**:704-9, p. 705, right column, "Softer surfaces and Tethering," lines 1-9). Boxer et al. further teach that "lipid bilayers and membrane proteins are notoriously difficult to work with" (ibid, p. 704, right column, lines 14-15). The instant specification discloses that "[o]bservations of labeled CTB indicate that it is relatively immobile when bound to supported membranes" (p. 34, lines 21-22). From the above teachings of Boxer et al., this may indicate that CTB is non-functional, and would therefore be incapable of interacting with test agents. This would be of particular relevance to claim 3, in which bacterial endotoxins may be

the lipid bilayer-associated component that interacts with test agents. The examiner notes that claim 3 is in contrast with the examples presented in the disclosure, in which CTB is the *test agent*, rather than the *lipid bilayer-associated component*. The specification does not disclose any working examples where CTB is the lipid bilayer-associated component. Further, if immobilized CTB is immobile, it is unclear how it would be able to aggregate (cluster) upon binding by a test agent, and therefore decrease membrane fluidity.

More generally, the specification does not provide direction regarding the preservation of function of integral membrane proteins or other lipid bilayer-associated components. There are no working examples of functional lipid bilayer-associated components that interact with test agents, other than ganglioside GM1.

In summary, the prior art as well as the post-filing literature cited in the Declaration filed 2/2/06 establishes that the test agent-component pair of CTB-ganglioside GM1 has particular characteristics (such as polyvalency and large size) that allow for indirect detection of interaction by changes in the membrane fluidity. However, these characteristics are not shared by all test agent-component pairs encompassed by the claims. The prior art also teaches the unpredictability of preparing functional lipid bilayer-associated components such as integral membrane proteins, as well as the unpredictability in observing changes in membrane fluidity upon binding by all test agents, especially those that are monovalent. Therefore, due to the state of the prior art, which teaches that not all test agents have effects on membrane fluidity, the lack of direction/guidance presented in the specification regarding detection of interactions by evaluation of physical properties where the test agent-component pairs are other than CTB/ GM1, the lack of working examples directed to same, and the breadth of the claims, the

specification fails to teach the skilled artisan how to make and use the claimed invention without undue experimentation.

17. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

18. Claims 4-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

19. Claim 4 recites a method according to claim 1, "further comprising a label **associated with** one or more of the lipid bilayer expanses". This terminology ("associated with") is vague and renders the claim indefinite because it is unclear in what manner the label is "associated with" the lipid bilayer expanses. The metes and bounds of the term are unclear.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. Claims 1-2, 4-7, 10, 34-36, 40 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boxer et al. (US Patent No. 6,228,326; referred to as "Boxer et al."), or, alternatively, by Boxer et al. (WO 98/23948; referred to as "Boxer '98"), which contains the same teachings, in view of Keinanen et al. (US 6,235,535 B1).

The column and line numbers discussed below refer to those in Boxer et al., US Patent No. 6,228,326, unless otherwise stated.

Boxer et al. teach methods of detecting interaction between a test agent and a lipid bilayer-associated component, involving a surface detector array device comprising a substrate having a surface defining a plurality of distinct bilayer-compatible surface regions separated by one or more bilayer barrier, where the bilayer-compatible surface regions and the bilayer barrier regions are formed of different materials (see the entire document, especially Figure 1; column 3, line 28 to column 4, line 43; and columns 15-18). The surface array detector device also comprises a plurality of lipid bilayer expanses located above the plurality of distinct bilayer-compatible surface regions, wherein the expanses are localized above the surface regions in the absence of covalent linkages to the surfaces and are separated from the surfaces by an aqueous film (column 3, lines 28-40).

Boxer et al. further teach that the device may be used in a method for detecting binding between a test agent and a lipid bilayer-associated component (column 4, lines 25-31 and 41-43; column 12, lines 12-15, 31-33 and 39-42; and column 15, line 65 to column 16, line 7), wherein a bulk aqueous phase comprising the test agent is contacted with the device (column 17, line 65 to column 8, line 5). In order to detect interaction between the test agent and the lipid bilayer-associated component, a physical property of a lipid bilayer expanse may be evaluated and correlated with binding of the test agent; for example, a change in the transmembrane voltage or current may be measured (column 18, lines 5-12) or changes in the bilayer environment surrounding a lipid bilayer-associated receptor in response to binding of a ligand may be detected by SPR (column 16, lines 11-38).

Boxer et al. and Boxer '98 teach evaluation of membrane fluidity by FRAP and by electrophoresis (column 6, lines 18-65; Examples 2-3). However, in Boxer et al. and Boxer '98, evaluation of membrane fluidity is performed as a separate experiment from the method for detecting binding between the test agent and the lipid bilayer-associated component. The evaluation is performed as a means of quality control, in order to assess whether the artificial supported bilayers are fluid.

Thus, the Boxer et al. references differ from the claimed invention in that they fail to specifically teach evaluating membrane fluidity *in order to detect binding between a test agent and a lipid bilayer-associated component.*

Keinanen et al. teach methods of detecting interaction between multivalent test agents and lipid bilayer-associated components (such as membrane-bound antibodies), in which binding is detected by detecting changes in the "aggregation level" of the lipid bilayer-associated components (see the entire document, especially at column 2, line 50 to column 3, line 4, line 7; and Figure 1). Specifically, binding of multivalent test agent induces microaggregation of the lipid bilayer-associated components, which can be detected by FRET. Keinanen et al. teach that this assay format allows for simple and easy detection in a homogeneous manner that does not require separation or wash steps (column 1, lines 15-29; column 2, lines 42-49). Although Keinanen et al. principally teach detection of binding by multivalent test agents, monovalent antigens can also be detected indirectly by the method (column 3, lines 30-41).

Keinanen et al. do not use the term "membrane fluidity" to describe the physical property that they are measuring. However, the "microaggregation" or "aggregation level" that is

measured in the reference is considered to be the same physical property as the claimed "membrane fluidity" based on statements made in Applicant's arguments (see p. 8-12).

Specifically, Applicant states that:

> The decrease in membrane fluidity results from cooperative binding between the test agent and the lipid bilayer-associated component, that is, ligand binding causes an aggregation of the membrane component (p. 9-10).

And elsewhere that:

> [l]igand binding causes an aggregation of the membrane component (p. 12)

Furthermore, the FRET technique used by Keinanen et al. to measure "aggregation" is also disclosed a suitable method of measuring "membrane fluidity" (see claim 10 and the specification at p. 15). For these reasons the examiner submits that Keinanen et al. are measuring one and the same property as Applicant, although they term it "aggregation" rather than "membrane fluidity".

Therefore, it would have been obvious to one of ordinary skill in the art to evaluate "aggregation" as taught by Keinanen et al. in the method of Boxer et al. or Boxer '98 in order to detecting binding of a multivalent test agent to the bilayer and also because Keinanen et al. teach that such a homogenous assay format allows for "simple and easy detection" without need for separation or washing steps.

With regard to claim 2, the supported bilayers of Boxer et al. may further comprise receptors including proteins or nucleic acids (column 4, lines 5-11 and column 12, lines 12-15 and 39-42 in particular).

With regard to claims 4-5, Boxer et al. teach that hexa-histidine tags may be attached to the ligands or receptors that are immobilized to the bilayer surface, as well as labels such as

avidin or streptavidin that may be coupled to biomolecules to link them to the supported bilayer (column 13, lines 36-59). Keinanen et al. also teach that the lipid bilayer-associated components are labeled with FRET donor and acceptor fluorophores (column 2, lines 56-62).

With regard to claim 6, Boxer et al. teach a device comprising lipid bilayers doped with the fluorescently labeled lipid probe Texas Red DHPE (column 14, lines 46-47; column 20, lines 15-28; column 21, lines 16-22 and 52-55). The Texas Red label is attached to a lipid bilayer-associated component (phosphatidylcholine) that does not specifically bind to a test agent, i.e., to a background membrane component (see the definition in the specification at p. 7, lines 1-2).

With respect to claim 7, Keinanen et al. teach that the membrane-bound antibodies are attached to fluorophores (see Figure 1).

With regard to claims 34-36 and 42, examples of test agents disclosed by Boxer et al. include the small molecule acetylcholine (column 18, lines 7-12), proteins (column 4, lines 5-9 and 26-31 and column 5, lines 16-30), and cells (column 18, lines 60-62). Keinanen et al. disclose test agents that are antibodies (column 3, lines 42-47), which are proteins and also "components" of cells/vesicles as in claim 36.

With respect to claim 40, Keinanen et al. also teach indirect immunoassay of monovalent antigens, in which case a second test agent (monovalent hapten) is added in the presence of the first test agent (Ox16BSA multivalent antigen) (column 3, lines 30-41 and column 10, line 64 to column 11, line 4). Keinanen teach that addition of the second test agent affected the interaction of the first test agent with the lipid-attached antibody, as there was a decrease in the fluorescence changes proportional to the amount of the added second test agent (column 11, lines 4-9).

21. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Boxer et al., or, alternatively, Boxer '98 in view of Keinanen et al. as applied to claim 1 above, and further in view of Gutsmann et al. ("Interaction of CAP18-Derived Peptides with Membranes Made from Endotoxins or Phospholipids," (2001) Biophysical Journal **80**:2935-2945).

Boxer et al. and Boxer '98 are as discussed above, which fail to teach a method wherein at least one lipid bilayer expanse further comprises a bacterial endotoxin.

Gutsmann et al. teach a method for assaying an interaction between a test agent (CAP18-derived peptides) with bacterial endotoxin (lipopolysaccharide) in differently composed lipid membranes (see the title; abstract; p. 2935, left column, the first paragraph; p. 2395, right column, the first full paragraph; and p. 2936, left column, second paragraph in particular). Gutsmann et al. teach that the reconstituted bilayers that comprise lipopolysaccharide mimic the outer membrane of Gram-negative bacteria (p. 2941, left column, lines 26-30) and such bilayers may be employed to assay interaction with the peptides by various biophysical techniques (p. 2941, left column, line 30 to right column, line 3 and the abstract, lines 11-12).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to employ bilayers comprising lipopolysaccharide, as taught by Gutsmann et al., in the method and device of Boxer et al. (or Boxer '98) and Keinanen et al., because Gutsmann et al. teach that such bilayers may be successfully employed in order to create a system that mimics the outer membrane of Gram-negative bacteria for use in methods to assay interaction of lipid bilayers with test agents, such as the methods of Boxer et al. and Boxer '98.

Double Patenting

22. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

23. Claims 1-2, 4-7, 10, 34-36, 40 and 42 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22-26 of U.S. Patent No. 6,699,719 (Yamazaki et al.) in view of in view of Keinanen et al.

Although the conflicting claims are not identical, they are not patentably distinct because Yamazaki et al. also claims a method comprising assaying an interaction between a test agent and a lipid-bilayer associated component using a surface detection array device (claim 22). The surface detection array device of Yamazaki et al. also comprises a substrate having a surface defining a plurality of distinct bilayer-compatible surface regions separated by one or more bilayer barrier regions that are formed of different materials, and wherein lipid bilayer expanses are localized above the bilayer-compatible surface regions. The method includes the step of contacting the device with a bulk aqueous phase comprising the test agent.

The claimed method of Yamazaki et al. fails to recite the step of evaluating the membrane fluidity of lipid bilayer expanses in order to detect the interaction.

Keinanen et al. teach methods of detecting interaction between multivalent test agents and lipid bilayer-associated components (such as membrane-bound antibodies), in which binding is detected by detecting changes in the "aggregation level" of the lipid bilayer-associated components (see the entire document, especially at column 2, line 50 to column 3, line 4, line 7; and Figure 1). Specifically, binding of multivalent test agent induces microaggregation of the lipid bilayer-associated components, which can be detected by FRET. Keinanen et al. teach that this assay format allows for simple and easy detection in a homogeneous manner that does not require separation or wash steps (column 1, lines 15-29; column 2, lines 42-49). Although Keinanen et al. principally teach detection of binding by multivalent test agents, monovalent antigens can also be detected indirectly by the method (column 3, lines 30-41).

Keinanen et al. do not use the term "membrane fluidity" to describe the physical property that they are measuring. However, the "microaggregation" or "aggregation level" that is measured in the reference is considered to be the same physical property as the claimed "membrane fluidity" as discussed above.

Therefore, it would have been obvious to one of ordinary skill in the art to evaluate "aggregation" as taught by Keinanen et al. in the method of Yamazaki et al. in order to detecting binding of a multivalent test agent to the bilayer and because Keinanen et al. teach that such a homogenous assay format allows for simple and easy detection without need for separation or washing steps.

Response to Arguments

24. Applicant's arguments filed 9/11/06 have been fully considered.

25. With respect to the rejections of claims 1-7, 10, 34-36, and 40 under 112, 1st paragraph (written description), Applicant's arguments (see p. 8-11) have been fully considered but they are not persuasive. Applicant argues that *cooperative* binding between a test agent and a lipid bilayer-associated component causes a decrease in membrane fluidity as a result of aggregation of the lipid bilayer-associated component upon binding by the test agent (see Applicant's response at the paragraph bridging p. 8-9). Applicant further argues that even if a ligand is not polyvalent, as long as it induces cooperative binding (aggregation) of the lipid bilayer-associated component, then there should be a decrease in membrane fluidity upon binding (p. 9).

These arguments are not persuasive because such statements relating to "cooperative" binding and "aggregation" of the lipid bilayer-associated component by the test agent are not described in the specification. The specification does not disclose selection of suitable test agents according to their ability to induce cooperative binding or receptor aggregation. The introduction of this relevant identifying characteristic of suitable test agents in Applicant's arguments fails to establish evidence of possession at the time of the invention when such an identifying characteristic has not been disclosed in the specification.

Furthermore, the examiner notes that the claims are not restricted to those test agents or "certain" small molecules that cause aggregation of a lipid bilayer-associated component, but are drawn to all proteins, small molecules, cells, and other agents. The specification does not describe suitable test agents in terms of their ability to bind cooperatively or to induce receptor aggregation, and therefore, such arguments post-filing are not relevant to a determination of

whether one skilled in the art would have understood the inventors, at the time the application was filed, had possession of the claimed invention *based on the specification.*

Applicant further argues that one skilled in the art would recognize that "cooperative binding **should work** with any test agent" (see the paragraph bridging p. 10-11; emphasis added), which is not found persuasive because the arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). In the instant case, the prior art of record teaches to the contrary, as Moran et al. report that binding of the test agent taurine has no effect on membrane fluidity (see above and the previous Office action at p. 10-12 with respect to scope of enablement). See also Altstiel et al. (discussed above), which teaches that monovalent ligands are "generally unable" to induce clustering (aggregation). Thus, the assertion that any test agent is capable of cooperative binding is unsupported by the evidence of record. Moreover, Applicant has not established that any agent capable of cooperative binding would also necessarily be capable of decreasing the membrane fluidity of a supported bilayer upon binding to a bilayer-associated component as claimed.

Applicant also cites three non-patent literature reference purported to disclose small molecules that can induce oligomerization/aggregation of G protein-coupled receptors as evidence that "**certain** small molecules" can induce receptor aggregation (and therefore, presumably, decreased membrane fluidity) (p. 9, emphasis added). However, because copies of the references were not supplied with the amendment, they have not been considered by the examiner. Nonetheless, the fact that there may be examples of small molecules that have the capacity to induce receptor aggregation fails to convey evidence of possession given that the specification does not disclose the concept of "small molecules that induce receptor

aggregation". As noted above, the specification fails to disclose relevant identifying characteristics of small molecules (or test agents generally) that are correlated with function, i.e. ability to decrease membrane fluidity upon binding.

26. With respect to the rejections of claims 1-7, 10, 34-36, and 40 under 112, 1st paragraph (scope of enablement), Applicant's arguments (see p. 11-12) have been fully considered but they are not persuasive. Applicant argues that the specification provides guidance for an exemplary polyvalent test agent (cholera toxin), and note that Applicant believes that cooperative binding between the test agent and the lipid bilayer-associated component causes aggregation (p. 12). Applicant's post-filing arguments are not on point because it is the *specification* that must supply the enabling aspects of the invention. Although the specification discloses the test agent cholera toxin, which happens to be polyvalent, the specification provides no direction or guidance to the effect that that test agents should be selected on the basis of their polyvalency and/or on the basis of their ability to bind cooperatively and induce aggregation. Furthermore, it is noted that the claims are not limited in scope to those test agents that are polyvalent and/or those that cooperatively bind to induce aggregation.

27. With respect to the rejections under 35 USC 103(a) set forth in the previous Office action, Applicant's arguments (see p. 13-16) have been considered but are moot in light of the new grounds of rejection.

28. With respect to the rejections under the judicially created doctrine of obviousness-type double patenting, Applicant's arguments (see p. 17-18) have been considered but are moot in light of the new grounds of rejection.

Conclusion

29. No claims are allowed.

30. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Lahiri et al. (US 6,977,155 B2) discloses methods of indirectly detecting binding of test agents to supported bilayers by detecting changes in physical properties of the membrane, including by detecting changes in the refractive index or electrical impedence (see especially at column 10, line 57 to column 11, line 18). However, the reference fails to teach methods of detecting binding by detecting changes in membrane fluidity.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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